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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/024,648	12/19/2001	Heather J. Belmont	49663 (71758)	2636

21874 7590 09/22/2008

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EXAMINER	
WEHBE, ANNE MARIE SABRINA	

ART UNIT	PAPER NUMBER
1633	

MAIL DATE	DELIVERY MODE
09/22/2008	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/024,648	BELMONT ET AL.	
	Examiner	Art Unit	
	Anne Marie S. Wehbe	1633	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *12 June 2008*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-118* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1,2,4-7,30,31,38,39,41-45,47 and 112-118* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED ACTION

Applicant's amendment and response received on 6/12/08 has been entered. Claims 3, 8-29, 32-37, 40, 46, and 48-111 are canceled. New claims 115-118 have been added. Claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 are pending and currently under examination. An action on the merits follows.

Those sections of Title 35, US code, not included in this action can be found in a previous office action.

It is again noted that claims 1-2, 4-7, 30-31, 38-39, 41-45, 47, and 112-118 continue to read broadly on any non-human transgenic animal. The claims have been and continue to be examined in view of the elected subject matter, i.e. a transgenic mouse. It is further noted that the species of mouse was elected **without** traverse, and that neither the elected species nor the generic claims are found to be allowable.

Claim Rejections - 35 USC § 103

The rejection of claims 1-2, 4-7, 30-31, 38-39, 41-47, and 112-114 under 35 U.S.C. 103(a) as being unpatentable over 5,859,312 (1/12/99), hereafter referred to as Littman et al. in view of Mombaerts et al. (1993) Cell, Vol. 75, 275-282, McMurry et al. (1997) Mol. Cell. Biol., Vol. 17 (8), 4553-4561, Rowen et al. (1996) Science, Vol. 272, 1755-1762, and Rack et al.

(1997) Blood, Vol. 90(3), 1233-1240, is maintained and further applied to new claims 115-118. Applicant's addition of new claims 115-118 necessitated their addition to this rejection. Applicant's amendments and arguments have been fully considered but have not been found persuasive in overcoming the rejection for reasons of record as discussed in detail below.

The applicant argues that the claims have now been amended to recite that the unrearranged human TCR alpha and beta loci undergo active rearrangement to encode a functional heterologous T-cell receptor and then reiterate their previous arguments that none of the cited references provide the requisite teaching of a mouse comprising human TCR loci that are capable of undergoing productive rearrangement, or a reasonable expectation of success in producing such as mouse based on differences between allelic exclusion in IgG heavy and light chain genes and TCR alpha and beta chain genes, and differences in B and T cell development, citing references by Sleckman et al. and Kruisbeek et al..

Specifically, the applicant argues that the constructs taught by McMurry et al. were designed with mutated V gene segments such that the rearranged TCR transgene does not express functional TCR protein products, and that Sleckman et al. and Kruisbeek et al. provide evidence that T cell development is different from B cell development such that no reasonable expectation of success could be extrapolated from transgenic mice comprising human Ig loci. In response, contrary to applicant's assertions, B cell development and T cell development are remarkably similar. Hardy et al. for example sets forth the various stages of B cell development which parallel to a large degree those T cell development as set forth in Kruisbeek et al. Please note that Hardy et al. is cited here for the sole purpose of rebutting applicant's arguments based on the newly cited Sleckman and Kruisbeek publications provided with applicant's response.

Pre-B cells rearrange the Ig heavy chain locus and express a pre-B cell receptor comprising the rearranged Ig heavy chain and a lambda 5/VpreB surrogate light chain just as T cells rearrange the TCR beta locus and express a pre-T cell receptor comprising the rearranged TCR beta chain and pTalpha/ VpreT surrogate alpha chain (Hardy et al. (2001) Annu. Rev. Immunol., Vol. 19, 595-621, see pages 599-600, and Kruisbeek et al., page 639, Figure 2). Signaling through each of these pre-receptors results in both cessation of further rearrangement of the heavy chain or beta chain resulting in allelic exclusion, and maturation to the next stage of B or T cell development, which is the rearrangement of the Ig light chain loci or the TCR alpha locus (Hardy et al., pages 600-601, Kruisbeek et al., page 637, and Sleckman et al., page 1465). Further stages in development are likewise similar, including positive and negative selection of B and T cells. As such, applicant's argument that there is nothing in the transgenic IgG mouse literature to teach or suggest that an unrearranged human TCR beta locus could generate a human TCR beta chain capable of forming a functional complex with pTalpha chain to permit proper T cell development and T cell maturation, is not persuasive as the evidence of record as discussed in previous office actions shows that at the time of filing human unrearranged Ig heavy chain loci were fully capable of productive rearrangement in mice and that functional, fully developed B cells expressing human Ig and capable of responding normally to antigen stimulation were produced in these mice. Such, evidence shows that clearly the human Ig heavy chain at the pre-B cell stage was capable of forming a functional complex with lambda 5 and VpreB to allow development beyond the pre-B cell stage. Thus, based on the state of the art at the time of filing, and the clear parallels and similarities between B cell and T cell development as discussed above, it is maintained that the skilled artisan would in fact have had a reasonable

expectation that transgenic mice comprising unrearranged TCR beta and alpha loci would in fact be capable of rearranging these loci appropriately and further capable of developing mature T cells expressing functional alpha/beta TCR. The applicant is reminded that obviousness does not require absolute predictability of success; for obviousness under 35 U.S.C. § 103, all that is required is a reasonable expectation of success. See *In re O'Farrell,* 7 USPQ2d 1673 (CAFC 1988).

In addition, regarding the teachings of McMurry, the previous office action discussed the fact that the original Lauzurica and Krangel publication, which gives the first description of the transgenic mice comprising a human TCR delta locus used by McMurry, specifically states the reason why the mutations to the V gene segments in the construct were added. On page 45, under the heading "strategy", the authors state, "[w]e wanted the construct to serve as an innocuous reporter that would not influence the rearrangement of endogenous TCR genes via the process of allelic exclusion" (Lauzurica and Krangel (January, 1994), Vol. 179, 43-55- page 45). Thus, contrary to applicant's arguments, McMurry, as evidenced by the original Lauzurica and Krangel paper published in January of 1994 cited in McMurry et al., does not teach or suggest the expression of a human TCR would negatively influence thymic development. Instead, the authors of Lauzurica and Krangel and McMurry et al. were trying to answer the question of whether some precommitment to the alpha/beta or gamma/delta cell lineage dictates gene rearrangement or whether gene rearrangement dictates cell lineage development. Further, the fact that they felt the need to mutate the V region genes in the human TCR transgene construct indicates that the authors clearly expected that transgenic mice comprising the human TCR delta transgene would in fact productively rearrange this loci and express human TCR delta chains

thus inducing allelic exclusion. Therefore, the applicant's arguments regarding the teachings of McMurry et al. are not persuasive.

Finally, the applicant argues that claims 114 and 115 recite the limitation that the transgenic animals comprises a human TCR alpha locus which contains all the human TCR alpha V, J , and C genes, and further a human TCR beta locus which contains all the human TCR beta V, J, and C genes. In response, it is noted that in fact claims 114 and 115 do not contain such limitations. Claim 114 as amended recites that the human TCR alpha locus contains human TCR V, J, and C genes. New claim 115 recites that the human TCR beta locus contains human TCR beta V, D, J, and C genes. There are no limitations in either claim that all V, (D), J, and C gene elements be present in the human TCR alpha or beta loci present in the transgenic animals. As such, applicant's argument is unpersuasive.

Therefore, for reasons of record and the discussion above, the rejection stands.

Claim Rejections - 35 USC § 112

The rejection of claim 114 under 35 U.S.C. 112, second paragraph, for indefiniteness is withdrawn in view of the amendments to claim 114.

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL**. See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Any inquiry concerning this communication from the examiner should be directed to Anne Marie S. Wehbé, Ph.D., whose telephone number is (571) 272-0737. If the examiner is not available, the examiner's supervisor, Joseph Woitach, can be reached at (571) 272-0739. For all official communications, **the new technology center fax number is (571) 273-8300**. Please note that all official communications and responses sent by fax must be directed to the technology center fax number. For informal, non-official communications only, the examiner's direct fax number is (571) 273-0737. For any inquiry of a general nature, please call (571) 272-0547.

The applicant can also consult the USPTO's Patent Application Information Retrieval system (PAIR) on the internet for patent application status and history information, and for electronic images of applications. For questions or problems related to PAIR, please call the USPTO Patent Electronic Business Center (Patent EBC) toll free at 1-866-217-9197.

Representatives are available daily from 6am to midnight (EST). When calling please have your application serial number or patent number available. For all other customer support, please call the USPTO call center (UCC) at 1-800-786-9199.

Dr. A.M.S. Wehbé

/Anne Marie S. Wehbé/
Primary Examiner, A.U. 1633